

# Importance of Sugar Chains in the Function of Growth Factor Receptors

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## Introduction

Growth of normal cells in our body is strictly controlled on demand, and proceeds, e.g., under conditions of wound healing and recovery from inflammation of tissues. Usually, normal cells do not freely grow without appropriate external signals. Such signals are often mediated by proteins known as growth factors. Although these proteins cannot translocate across the plasma membrane, integral membrane receptor proteins receive the extracellular signals through binding growth factors and transmit the signal of growth into the intracellular space. Many receptor proteins are glycosylated, and the addition of sugar chains appears to confer expression of functional receptors. If the receptors do not correctly trigger transmembrane signaling, the proteins may instead activate the intracellular signaling pathways, in spite of the absence of an extracellular signal, causing abnormal cell growth. Thus, loss of normal receptor function could lead to a malignant alteration of cells.

Epidermal growth factor (EGF) stimulates cell growth by binding to EGF receptor localized on the cell surface. The EGF receptor is a single-transmembrane spanning protein, and is composed of extracellular-, transmembrane- and intracellular-domains. EGF, as a ligand for the receptor, first binds to the extracellular domain, and then induces the conformational change of the receptor protein, which leads to dimerization of the receptor. The resulting close proximity of the two intracellular domains permits mutual phosphorylation of tyrosine residues in the domains by intrinsic kinase activity. This process is known as autophosphorylation of the receptor and is the first step in intracellular growth signaling.

It has been found that N-glycosylation plays an essential role in the function of the EGF receptor (Tsuda et al. 2000; Wang et al. 2001). The loss of the specific sugar chain in the receptor impairs the EGF-directed dimerization of the receptor. As reported, even in the absence of EGF, the mutant receptor, which lacks only a single N-linked sugar chain, spontaneously clusters to form a homo-oligomer, which eventually causes receptor autophosphorylation (Tsuda et al. 2000). These findings suggest that alteration of sugar chains in the growth factor receptor can potentially disrupt regulation of cell growth, although it may or may not transform the cells into malignant cells.

## Concept

It is well known that genetic alterations of genes encoding growth factor receptors yield mutant receptors that activate intracellular signal transduction pathways for cell growth without appropriate extracellular stimuli. Such mutated genes are often referred as oncogenes and have been extensively investigated. As described above, however, normal functions of the receptors are conferred not only by polypeptides but also by added sugar chains. Thus, sugar chains in the glycoproteins are as important as the polypeptide portion, in terms of expression of functional receptors. Further study on the involvement of sugar chains in the receptor function will enhance their importance.

## References

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